Dolutegravir used in real-life provides high rates of virological response in conjunction with a rare emergence of integrase resistance.

D. Armenia\textsuperscript{1}, V. Borghi\textsuperscript{2}, F Forbici\textsuperscript{3}, C. Gori\textsuperscript{3}, A. Bertoli\textsuperscript{1}, D. Di Carlo\textsuperscript{1}, W Gennari\textsuperscript{2}, R. Bellagamba\textsuperscript{3}, A. Vergori\textsuperscript{3}, M Colafigli\textsuperscript{4}, G. Maffongelli\textsuperscript{5}, C. Mussini\textsuperscript{2}, M. Andreoni\textsuperscript{5}, A. Antinori\textsuperscript{3}, F. Ceccherini-Silberstein\textsuperscript{1}, C.F. Perno\textsuperscript{2}, M.M. Santoro\textsuperscript{1}

\textsuperscript{1}University of Rome “Tor Vergata”, Rome, Italy. \textsuperscript{2}Polyclinic of Modena, Modena, Italy. \textsuperscript{3}L. Spallanzani Hospital, IRCSS, Rome, Italy. \textsuperscript{4}IRCSS San Gallicano, Italy. \textsuperscript{5}University Hospital Tor Vergata, Rome, Italy.

• However, data about virological response and resistance profile of this second generation integrase inhibitor (INI) are few in clinical setting.
Aim

We evaluated the virological response and resistance profiles of dolutegravir in real-life.
Data from patients in care for HIV-1 infection with an available viremia follow-up after starting a dolutegravir containing regimen were examined. Two groups of patients were evaluated:

- **Viremic patients:** cART naïve and cART experienced patients (INI-naïve or INI-experienced) with detectable viremia at baseline.

- **Virologically suppressed patients:** cART experienced patients (INI naïve or INI-experienced) with viremia <50 copies/mL at baseline.

Kaplan Meyer estimates were used to evaluate the probability of virological success (VS: viremia <50 copies/ml) and virological rebound (VR50: two consecutive viremia >50 copies/mL or one >1000 copies/mL; VR200: two consecutive viremia >200 copies/mL) under dolutegravir-treatment. Previous resistance and its evolution at virological failure (defined as viremia >50 copies/mL under dolutegravir treatment if virological undetectability was never achieved or after the achievement of virological success) were also evaluated. Major resistance mutations (MRMs) and accessory resistance mutations (ARMs) were evaluated according to the IAS/Stanford resistance lists 2017.
Results:

Viremic patients
The table provides characteristics of viremic patients treated with dolutegravir. The number of patients treated with dolutegravir (N=201) is listed along with the median year of starting treatment and the interquartile range (IQR) of 2015-2016.

### Previous cART Exposure

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naïve</td>
<td>78</td>
<td>38.1%</td>
</tr>
<tr>
<td>cART-experienced INI-naive</td>
<td>55</td>
<td>27.3%</td>
</tr>
<tr>
<td>INI-experienced</td>
<td>68</td>
<td>33.8%</td>
</tr>
</tbody>
</table>

### Previous Drug-Class Resistance

<table>
<thead>
<tr>
<th>Level</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>87</td>
<td>43.3%</td>
</tr>
<tr>
<td>1</td>
<td>42</td>
<td>20.9%</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>12.9%</td>
</tr>
<tr>
<td>≥3</td>
<td>24</td>
<td>11.9%</td>
</tr>
<tr>
<td>Unknown</td>
<td>22</td>
<td>10.9%</td>
</tr>
</tbody>
</table>

### Time Under cART (years), Median (IQR)

- Median time under cART: 1 year (IQR: 0-13)

### No. of Previous Regimens Received, Median (IQR)

- Median number of previous regimens: 1 (IQR: 0-6)

### No. of Antiretroviral Classes Previously Received, Median (IQR)

- Median number of antiretroviral classes: 2 (IQR: 0-4)

The bar chart illustrates the distribution of the number of drugs administered in the dolutegravir containing regimen. The most common combinations include FTC+TDF (43.6%), ABC+3TC (32.2%), and DRV (17.3%). Other drugs and categories are also shown.
By 12 months after dolutegravir start the probability of achieving VS was 84%. INI-experienced patients showed a lower probability of VS compared to those INI-naive.

Keplan Meyer estimates of achieving VS

Median time of VS (95% CI)
2.3 (2.0-2.6) months

VS: virological success (achievement of viremia <50 copies/mL after treatment start); CI: Confidence interval. IQR: interquartile range
By 12 months after dolutegravir start the probability of achieving VS was 84%. INI-experienced patients showed a lower probability of VS compared to those INI-naive.

**Kaplan Meyer estimates of achieving VS**

- **INI-naive**
  - Median time of VS (95% CI): 2.3 (2.0-2.6) months
  - Probability of achieving VS at 12 months: 84%

- **INI-experienced**
  - Median time of VS (95% CI): 2.1 (1.7-2.5) months
  - Probability of achieving VS at 12 months: 76%

**VS:** virological success (achievement of viremia <50 copies/mL after treatment start); CI: Confidence interval. IQR: interquartile range
By 24 months from the achievement of VS the probability of experiencing VR50 was 25%. INI-experienced patients showed a higher probability of experiencing VR50 compared to those INI-naive. At rebound viremia level was very low.

Keplan Meyer estimates of experiencing VR50

INI-naive
INI-experienced

Viremia at VR (copies/mL), Median (IQR):
116 (75-284)
136 (72-17,058)

P=0.041

VR50: two consecutive viremia >50 copies/mL or one >1000 copies/mL;
By 24 months from the achievement of VS the probability of achieving VR200 was 10%. No difference according with INI-exposure was found.

Keplan Meyer estimates of experiencing VR50

INI-naive | INI-experienced
---|---
P=0.041

Viremia at VR (copies/mL), Median (IQR):

- VR50: 116 (75-284)
- VR50: 136 (72-17,058)

Keplan Meyer estimates of experiencing VR200

INI-naive | INI-experienced
---|---
P=0.399

Viremia at VR (copies/mL), Median (IQR):

- VR200: 1,304 (272-28,231)
- VR200: 22,238 (2,605-68,246)

VR50: two consecutive viremia >50 copies/mL or one >1000 copies/mL; VR200: two consecutive viremia >200 copies/mL. IQR: interquartile range
Results:

Virologically suppressed patients
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Viremic patients (N=296)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year of starting treatment, Median (IQR)</strong></td>
<td>2016 (2015-2016)</td>
</tr>
<tr>
<td><strong>Time under virological suppression (years), Median (IQR)</strong></td>
<td>4.9 (1.7-8.2)</td>
</tr>
<tr>
<td><strong>Previous cART exposure</strong></td>
<td></td>
</tr>
<tr>
<td>cART-experienced INI-naive</td>
<td>167 (56.4)</td>
</tr>
<tr>
<td>INI-experienced</td>
<td>104 (35.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>25 (8.4)</td>
</tr>
<tr>
<td><strong>Previous drug-class resistance, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>117 (39.5)</td>
</tr>
<tr>
<td>1</td>
<td>43 (14.5)</td>
</tr>
<tr>
<td>2</td>
<td>51 (17.2)</td>
</tr>
<tr>
<td>≥3</td>
<td>34 (11.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>51 (17.2)</td>
</tr>
<tr>
<td><strong>Time under cART (years), median (IQR)(^a)</strong></td>
<td>12 (5-19)</td>
</tr>
<tr>
<td><strong>No. of previous regimens received, Median (IQR) (N=271)</strong></td>
<td>5 (2-9)</td>
</tr>
<tr>
<td><strong>No. of antiretroviral classes previously received, Median (IQR) (N=271)</strong></td>
<td>3 (2-4)</td>
</tr>
</tbody>
</table>

### Drugs administered in dolutegravir containing regimen

<table>
<thead>
<tr>
<th>No. of drugs in the regimen</th>
<th>NRTIs</th>
<th>PIs</th>
<th>NNRTI</th>
<th>EI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>54.2</td>
<td>43.5</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>34.8</td>
<td>29.1</td>
<td>17.2</td>
<td>13.9</td>
</tr>
<tr>
<td>&gt;3</td>
<td>17.2</td>
<td>13.9</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>only ABC+3TC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>only Nuc-Sparing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTC+TDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRV</td>
<td>8.4</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ATV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPV</td>
<td>8.8</td>
<td>0.7</td>
<td>0.3</td>
<td>3.7</td>
</tr>
<tr>
<td>ETR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
By 24 months from the dolutegravir switching the probability of experiencing VR50 and VR200 was 12% and 4%, respectively. No significant difference was observed by stratifying patients according to INI exposure.

Kaplan-Meier estimates of experiencing VR50*

Viremia at VR (copies/mL), Median (IQR):
- VR50: two consecutive viremia >50 copies/mL or one >1000 copies/mL
- VR200: two consecutive viremia >200 copies/mL

P=0.826

Kaplan-Meier estimates of experiencing VR200*

Viremia at VR (copies/mL), Median (IQR):
- VR50: two consecutive viremia >50 copies/mL or one >1000 copies/mL
- VR200: two consecutive viremia >200 copies/mL

P=0.565

*Performed on 271 patients with available treatment history information
By 24 months from the dolutegravir switch, longer was the previous time of virological suppression lower was the probability of experiencing rebound.

Kaplan Meyer estimates of experiencing VR50

P=0.007

Kaplan Meyer estimates of experiencing VR200

P<0.001

VR50: two consecutive viremia >50 copies/mL or one >1000 copies/mL; VR200: two consecutive viremia >200 copies/mL; IQR: interquartile range
By 24 months from the dolutegravir switch, longer was the previous time of virological suppression lower was the probability of experiencing rebound. No events of VR200 was observed among patients with >3 years of previous suppression.

VR50: two consecutive viremia >50 copies/mL or one >1000 copies/mL; VR200: two consecutive viremia >200 copies/mL; IQR: interquartile range
Among 26 patients with an available integrase GRT at virological failure, only 7 (27%), mainly multi-experienced and resistant to first-generation INIs, developed IN major resistance mutations. T97A, E138K/T, G140A, S147G, Q148R and N155H MRMs were selected under dolutegravir pressure.

<table>
<thead>
<tr>
<th>Patients’ category</th>
<th>ID</th>
<th>Previous ARV classes experienced</th>
<th>Previous INI failure</th>
<th>Previous INI MRMs&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Previous INI ARM&lt;sup&gt;e&lt;/sup&gt;</th>
<th>Viremia at GRT (copies/mL)</th>
<th>Time under DTG treatment (months)</th>
<th>INI MRMs at failure&lt;sup&gt;c&lt;/sup&gt;</th>
<th>INI ARM at failure&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viremic&lt;sup&gt;a&lt;/sup&gt; (N=21)</strong></td>
<td>18</td>
<td>NRTI, NNRTI, PI, INI, FI, CCR5-An</td>
<td>RAL</td>
<td>G140S, Q148H</td>
<td>None</td>
<td>23,867</td>
<td>12</td>
<td><strong>E138K, G140S Q148H</strong></td>
<td>T97A</td>
</tr>
<tr>
<td></td>
<td>17524</td>
<td>NRTI, NNRTI, PI, INI, CCR5-An</td>
<td>EVG</td>
<td>Unknown</td>
<td>Unknown</td>
<td>23,000</td>
<td>2</td>
<td>G140S, Q148H</td>
<td>T97A</td>
</tr>
<tr>
<td></td>
<td>1166</td>
<td>NRTI, NNRTI, PI, INI, CCR5-An</td>
<td>RAL</td>
<td>G140S, Q148H, Y143C</td>
<td>T97A, E138K, S230R</td>
<td>3,965</td>
<td>5</td>
<td><strong>E138EAKT, G140S, Q148H, N155H</strong></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>11195</td>
<td>NRTI, NNRTI, PI, INI, CCR5-An</td>
<td>RAL</td>
<td>N155H, R263K</td>
<td>T97A</td>
<td>344,261</td>
<td>15</td>
<td><strong>E138K, G140A, S147G, Q148R</strong></td>
<td>T97A</td>
</tr>
<tr>
<td></td>
<td>12397</td>
<td>NRTI, NNRTI, PI, INI, CCR5-An</td>
<td>RAL</td>
<td>G140S, Q148H</td>
<td>E138A</td>
<td>26,891</td>
<td>15</td>
<td><strong>E138A, G140S, Q148H, N155H</strong></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>14808</td>
<td>NRTI, NNRTI, PI, INI, CCR5-An</td>
<td>RAL</td>
<td>G140S, Q148H</td>
<td>None</td>
<td>85,010</td>
<td>24</td>
<td>G140S, Q148H</td>
<td><strong>E138T, T97A</strong></td>
</tr>
<tr>
<td><strong>Virologically suppressed&lt;sup&gt;b&lt;/sup&gt; (N=5)</strong></td>
<td>17907</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>803</td>
<td>18</td>
<td>G140S, Q148QH</td>
<td>None</td>
</tr>
</tbody>
</table>

In bold red underlined: mutations selected under DTG pressure.

<sup>a</sup>Among 201 viremic patients starting DTG treatment, 21 had an available GRT at virological failure (viremia>50 copies/mL under dolutegravir treatment). <sup>b</sup>Among 296 virological suppressed patients switching to DTG based regimen, 5 had an available GRT at virological failure. <sup>c</sup>Resistance evaluated through HIV-DB algorithm ver 8.4. ARM: accessory resistance mutation; ARV: antiretroviral; CCR5-An: CCR5 antagonist; DTG: dolutegravir; FI: fusion inhibitor; GRT: genotypic resistance test; INI: integrase inhibitor; MRM: Major resistance mutation; NRTI: nucleot(s)ide reverse transcriptase inhibitor; NNRTI: non-NRTI; PI: protease inhibitor.
The use of dolutegravir in real-life results in high rates of virological response in all settings analyzed.

Despite the high rate of virological suppression, viremic patients with a previous history of INI failures are more prone to loss virological control under dolutegravir treatment.

Resistance at failure is rare and related with previous history of failures to first generation INIs.
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Policlinic of Rome Tor Vergata, Rome Italy
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L. Dori
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INMI L Spallanzani, Rome, Italy
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San Gallicano Hospital, Italy
M. Giuliani A. Pacifici
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- The Patients

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